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Editorial

Subphenotyping hypotension in early sepsis: A physiology-guided therapeutic approach

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Introduction

Severe arterial hypotension in septic patients should be corrected promptly as low mean arterial pressure (MAP) is associated with poor outcomes (1). Initiating appropriate treatment early remains a critical challenge since sepsis-induced hypotension may result from absolute hypovolemia, depressed vascular tone, cardiac dysfunction or a variable combination of mechanisms. Historically, management has emphasized early aggressive fluid resuscitation to restore intravascular volume with the goal of improving tissue perfusion. However, this uniform approach may be suboptimal since fluid administration often fail to correct severe hypotension when vasoplegia is predominant. Moreover, growing evidence indicates that fluid accumulation is associated with worse outcomes (2). These concerns underscore the need for early subphenotype-tailored therapeutic strategy in sepsis-induced hypotension.

Which bedside variables can clinicians use to guide immediate therapy in sepsis-induced hypotension?

- **Capillary Refill Time (CRT)**: A simple marker of peripheral perfusion (3). While CRT alone does not define a hypotension subphenotype, it is central to decision-making. A prolonged CRT indicates the need for therapy, whereas a normal CRT may suggest that correction of hypotension is unnecessary unless other clinical signs of hypoperfusion (e.g., altered mental status) are present. Moreover, CRT response to therapeutic tests (e.g., fluids, vasopressors) helps identify the underlying mechanism and guide whether the therapeutic plan should be continued or changed (3).
- **Pulse pressure (PP)**: A low PP reflects reduced stroke volume (SV) (4). However, PP is also influenced by arterial stiffness. In older patients or those with chronic hypertension or diabetes, an "apparently normal" PP (40–50 mmHg) may in fact indicate reduced SV (4).
- **Diastolic arterial pressure (DAP)**: Except in bradycardia, a low DAP (< 45–50 mmHg) strongly suggests decreased vascular tone (5).
- **Diastolic shock index (DSI)**: A high DSI (> 3) suggests severe vasodilation, even more reliably than a low DAP (6).

Pathophysiological subphenotypes of sepsis-induced hypotension

Three subphenotypes of sepsis-induced hypotension can be schematically distinguished (Table 1).

- ***Hypovolemic subphenotype***

✓ **Mechanism**: Absolute hypovolemia associated with the infectious state, typically with preserved vascular tone.

✓ **Hemodynamics**: reduced cardiac output (CO) secondary to decreased SV, resulting in lower pulse pressure (PP), and subsequently MAP. Heart rate (HR) is typically elevated as a compensatory mechanism. DAP is typically not reduced if vascular tone is preserved.

✓ **Therapeutic response**: When hypotension is accompanied by peripheral hypoperfusion, fluid resuscitation is logical to increase stressed blood volume, venous return, and SV. This can restore MAP and, eventually, peripheral perfusion.

Table 1
Main typical pathophysiological subphenotypes of sepsis-induced hypotension: macrohemodynamic features and initial therapeutic management.

Subphenotype	Mechanism	DAP	PP	MAP	Therapeutic management
Hypovolemic	↓ Absolute blood volume	normal	low	low	Fluids
Depressed vascular tone	↓ Arterial and venous tone	very low	normal	very low	Vasopressors
Cardiac dysfunction	↓ Myocardial contractility	normal	low	low	Inotropes

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- ***Depressed vascular tone subphenotype***

✓ **Mechanism**: Marked reduction in arterial and venous tone. Venous dilation contributes to relative hypovolemia through redistribution from stressed to unstressed blood volume.

✓ **Hemodynamics**: Reduced DAP and elevated diastolic shock index (DSI = HR/DAP) due to low arterial tone. MAP is low. CO is variable depending on the degree of relative hypovolemia related to decreased venous tone.

✓ **Therapeutic response**: If hypotension is accompanied by peripheral hypoperfusion, norepinephrine is the treatment of choice. Through its α_1-adrenergic effects, norepinephrine increases arterial tone (raising DAP and MAP) and venous tone (mobilizing blood into the stressed compartment) (7), thereby addressing both hypotension and relative hypovolemia.

- ***Cardiac dysfunction subphenotype***

✓ **Mechanism**: Sepsis-related myocardial depression with impaired contractility.

✓ **Hemodynamics**: Reduced SV and lower-than-normal PP, low MAP but relatively preserved DAP due to intact vascular tone. This profile may be difficult to distinguish from hypovolemia. Other factors such as anamnestic context, prior cardiac disease, cardiovascular comorbidities, associated clinical findings (e.g., pulmonary edema), help diagnose the cardiac dysfunction subphenotype, which should ideally be confirmed by echocardiography.

✓ **Therapeutic response**: When this subphenotype is recognized as predominant and hypotension accompanied by peripheral hypoperfusion, inotropic support should be considered.

Mixed subphenotypes

In most septic patients, hypotension results from a combination of the three primary subphenotypes rather than from a single mechanism. A common example is combined hypovolemia and vasoplegia, characterized by both reduced PP and reduced DAP. The logical therapy combines fluids (to correct absolute hypovolemia) and norepinephrine (to restore vascular tone). Delaying norepinephrine in this setting is risky, as fluids alone may worsen vasodilation (8). Early norepinephrine promptly restores MAP and mobilizes venous blood, while fluids correct the component of low flow due to absolute hypovolemia (7). Other possible patterns include combination of cardiac dysfunction with vasoplegia or with hypovolemia. Before initiating an inotrope such as dobutamine, 1) the diagnosis of cardiac dysfunction should be well established (relying on the other signs described above), and 2) any associated hypovolemia and vasoplegia should be corrected, since such a treatment may be poorly tolerated and can particularly worsen vasoplegia (9). Finally, some patients exhibit contributions from all three mechanisms in varying proportions. Importantly, these proportions are not fixed: they may vary over time, with subphenotypes emerging, receding, or combining to different degrees as the clinical course evolves.

Beyond early subphenotyping

While early subphenotyping is critical, it cannot by itself define the entire resuscitation strategy. Additional considerations—such as MAP targets (including critical closing pressure), fluid responsiveness or intolerance, vasopressor responsiveness or intolerance, and evolving microcirculatory behavior—often necessitate ongoing adjustment of therapy, even when the initial subphenotype has been clearly identified (10).

Advanced clinical tools such as central venous oxygen saturation, the carbon dioxide pressure gap, indices of fluid responsiveness, indices of vascular tone responsiveness (11), and the VExUS score (12) provide guidance for subsequent management (13), which is inherently heterogeneous across patients. More invasive hemodynamic monitoring should be considered at a further step in complex cases unresponsive to initial therapy, especially when fluid benefit–risk balance must be carefully assessed (e.g., in severe ARDS). Integration of these hemodynamic variables supports the implementation of a personalized, patient-tailored approach (13).

Clinical implications and future directions

Subphenotyping sepsis-induced hypotension at the earliest phase of resuscitation is a key step toward precision resuscitation. When combined with clinical context, simple bedside markers (CRT, DAP, PP, MAP, DSI) help identify the predominant mechanism, enabling clinicians to administer fluids, vasopressors, inotropes, or their combination in a timely manner. The most recent evidence from the ANDROMEDA-SHOCK-2 trial showed that a CRT-targeted, physiology-guided resuscitation strategy improve outcomes (14), supporting the clinical value of pragmatic, physiology-based bedside algorithms.

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Carlos Sanchez E.[a,*], Jean-Louis Teboul[b]

[a] *Critical Care Medicine, Organ Transplant Center of Excellence, King Faisal Specialist Hospital & Research Centre. Riyadh, Saudi Arabia*
[b] *Faculté de Médecine Paris-Saclay, Université Paris-Saclay, Le Kremlin-Bicêtre, France*

* Corresponding author.
E-mail address: dr.carlossanchez@hotmail.com (C. Sanchez E.).